Technology Assessment Program

Office of Patient Care Services

UPDATED INFORMATION FOR VA TECHNOLOGY ASSESSMENT PROGRAM (VATAP) REPORTS

In June 2000, VATAP was relocated within the Veterans Health Administration from the Office of Research & Development to the Office of Patient Care Services. The following report was produced prior to the relocation of VATAP.

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Appendix 5

Systematic Review: PET as a Diagnostic Test in Breast Cancer

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Appendix 5

Systematic Review: PET as a Diagnostic Test in Breast Cancer

The final literature database searches for the systematic reviews were performed on September 10, 1996; the assessment represents peer-reviewed literature published and indexed as of that date.

This Appendix to the PET assessment presents the results of the systematic review of PET in breast cancer. A general rationale for the use of PET in oncology is supplied by Hawkins, et al. (1994) and Hoh, et al. (1994):

- many forms of cancer characteristically perturb tissue biochemical and physiological processes and PET imaging can be expected to detect the resulting abnormalities;
- reliance on tumor histology and anatomy limits the oncologist's tools for selecting optimal treatment;
- the ability to monitor metabolic responses to treatment could allow the early re-direction of therapy in patients who fail to respond to the first attempt at radiation or chemotherapy.

These and other authors (e.g., Price and Jones, 1995) report that PET studies in cancer are emerging as a major focus of the technology, both in basic research and in clinical investigations. Information gathered by the MDRC Technology Assessment Program from VA PET facilities corroborates that perception (see *Appendix 9: Experience With PET in VHA*).

Fluorine-18-fluorodeoxyglucose (FDG) is the most commonly employed radiopharmaceutical in PET cancer studies. Many neoplasms have high glycolytic rates, resulting in intracellularly trapped phosphorylated FDG that can be imaged with PET. Hawkins, et al. (1994), note that tumor-specific biochemical characteristics of glucose transport and phosphorylation may affect quantitative estimates of tumor glucose metabolism with FDG PET, and that investigations are under way to define these characteristics. However, these uncertainties may be of less concern with qualitative or semiquantitative FDG PET cancer studies because the primary intent of such studies is to detect and map tumor foci, not to rigorously quantify tumor glycolytic rates.

In some instances, PET imaging techniques have been modified to meet the needs of cancer diagnosis. Most PET systems allow axial fields of view (the length of the body encompassed by a series of cross sectional images) of approximately 10 cm. Cancer is frequently distributed beyond this field of view, and whole body image acquisition procedures have been developed (Hoh, et al., 1993). Since it is impractical to apply standard transmission scanning attenuation correction methods to these procedures, whole body PET imaging is primarily useful as a qualitative indicator of disease distribution.

Nieweg (1994) and Price and Jones (1995) define a number of potential applications for PET in oncology. These include:

- tumor detection (although PET images offer insufficient structural detail and should not be used to visualize anatomy; registration techniques to combine PET and anatomic imaging into a single image are under development to circumvent this limitation);
- staging (particularly using whole-body imaging methods) although there is a lower limit to the size of metastases that can be detected by PET;
- detection of local recurrence of disease, since anatomically-based imaging is often limited by the effects of treatment;
- prediction of tumor response to chemotherapy;
- treatment monitoring.

I. BACKGROUND

A. General sources

The discussion in this overview section, unless otherwise noted, is based on information distributed by the National Cancer Institute (NCI) in September, 1996 through its on-line Physician Data Query (PDQ) system.

B. Description

Breast cancer is the most common life-threatening malignancy among adult women in every major ethnic group in the United States (Kelsey and Horn-Ross, 1993). It is highly treatable by surgery, radiotherapy, chemotherapy, and hormonal therapy, and can be cured when detected in its early stages. Accordingly, screening programs using mammography and/or breast physical examination have been widely implemented and tested for efficacy.

C. Epidemiology

The American Cancer Society (Cancer Facts and Figures, 1996) estimates that 184,300 new cases will be diagnosed in 1996; approximately 1 of every 8 women (12.5%) will develop breast cancer during the course of a maximum life expectancy. A 4% per year increase in the incidence rate has been observed between 1982 and 1987; part of the increase may be attributable to screening programs which detect some breast cancers while they are still non-invasive (carcinoma in situ) and before they become clinically apparent (Liff, et al., 1991).

In 1992, there were 1,199,370 women veterans (4.4% of the total veteran population) (Department of Veterans Affairs, National Survey of Veterans, 1995). An HSR&D service-directed research project (Feussner and Hynes, abstract in: *Projects Receiving Funding in Fiscal Year 1995*) found an urgent need to promote early breast cancer detection program for women veterans and to further assess their risks for breast cancer.

Although the incidence of breast cancer is increasing, early detection by means of routine mammography examination and improved treatment have allowed the death rate to remain essentially unchanged since 1930. Breast cancer is now the second most common cause of cancer death among women (after lung cancer). Approximately 44,300 women and 260 men will die of breast cancer in the United States in 1996; 15% of these deaths will occur among premenopausal women, making breast cancer a leading cause of years of potential life lost.

The risk of breast cancer increases with age in high-risk areas such as the United States, but the increase with age is less steep after about age 45-50 than it is during the reproductive years. The specific factors associated with a three- to four-fold relative risk for the development of breast cancer include; first-degree relative (mother or sister) with breast cancer; prior breast cancer; nulliparity; first childbirth after age 30; early menarche or late menopause; and radiation exposure, particularly in the prepubertal years. Other factors implicated in increasing the risk for breast cancer include: hyperplastic fibrocystic disease with atypical epithelial cells; use of oral contraceptives by young women before a first pregnancy; long-term use of non-conjugated estrogens; and the fat content of the diet.

The etiology of breast cancer remains undefined. Some of the risks listed above may relate to etiology; genetic factors, hyper- or un- opposed estrogen activity over a long reproductive life span, and some dietary factors are thought to contribute.

D. Diagnosis

Invasive carcinomas of the breast can arise from both the lobular and ductal components of breast tissue. Approximately 85% of invasive carcinomas are infiltrating ductal carcinomas; 10% are infiltrating lobular carcinomas; and the remaining 5% include medullary, mucinous, tubular, and adenoid cystic histopathological varieties. Although use of mammography has reduced the average size of newly diagnosed breast lesions to 2.5 cm, many breast cancers are still discovered by patients or physicians during routine examinations (and are therefore clinically detectable at diagnosis). Currently, between 30% and 50% of breast cancer lesions have progressed to involve the axillary lymph nodes at diagnosis.

Following initial diagnosis, that diagnosis is confirmed, stage of disease is evaluated, and therapy is selected. Diagnosis may be confirmed by aspiration cytology, solid core needle biopsy, or incisional or excisional biopsy. When technically possible, an excisional biopsy both supplies material for definitive diagnosis of a breast lesion, and acts as the primary surgical treatment (which also includes axillary dissection) for a woman with a small primary tumor who will subsequently receive radiation therapy as her principal adjuvant therapy. Additional prognostic factors determined during the diagnostic process include stage of the disease, histologic and nuclear grade, and hormone receptor status.

E. Staging, treatment, and survival

The staging system for breast cancer provides a strategy for grouping patients with respect to prognosis. Both survival and risk of relapse after treatment are associated with the degree of progression of the disease at diagnosis. The size of the primary tumor, the presence or absence of histologically confirmed lymph node involvement, the number of nodes involved, and the metastatic spread of the disease at diagnosis and initial surgical treatment are used in staging (tumor, node, metastases, or TNM staging). Stage-specific survival rates have increased only slightly since the 1970s.

Breast cancer is a common cause of death among women, and a significant contributor to potential years of life lost. In order to reduce breast cancer mortality, a number of approaches could be taken. Since the cause of breast cancer remains elusive for the majority of women with the disease, primary prevention is not yet feasible. Screening programs attempt to identify early breast cancers when they are highly curable. Mammography (with/without clinical breast exam) is currently the best screening tool available, and has been shown to be of value in randomized trials. Combined Swedish trial data indicate that mammography produced an overall reduction in breast cancer mortality of 29% during 12 years of follow up in women over 50 and a 13% reduction in younger women (Blamey, et al., 1994), although screening in unselected populations of women under 50 remains controversial.

Finally, treatment for more advanced breast cancer can be improved. Currently, treatment is associated with less than optimal outcomes with respect to both survival and quality of life during treatment, and is an area of intense research activity. The NCI notes that, even when standard therapy is effective, patients with breast cancer are appropriately considered as candidates for clinical trials designed to improve therapeutic results and to decrease the morbidity of treatment.

Therapeutic decisions are made in part according to staging categories, but primarily according to lymph node status, estrogen and progesterone receptor levels in the tumor, menopausal status, and the overall health of the patient. In general, initial treatment for breast cancer is surgical removal of the tumor, followed by radiation therapy to enhance loco-regional control and/or by chemotherapy to reduce the risk of recurrence due to micrometastases or to control identified metastases. Table 1 provides information on the

TNM staging system in breast cancer, on the therapeutic options at each stage, and on survival.

The lifetime cost of treating breast cancer has been estimated at $61,000 in 1991 dollars (over $10 billion in the U.S. in 1991). These costs are only those borne by the medical care system; additional unquantified costs are associated with pain, suffering, and anxiety to patients and their families. The U.S. General Accounting Office has concluded that the best prospect for reducing breast cancer mortality is through increased utilization of screening mammography. Cost-effectiveness studies estimate that mammography has a marginal cost of approximately $36,000 (over clinical breast exam alone) per year of life saved, which is comparable to the cost effectiveness of treating hypertension and hypercholesterolemia (White, et al., 1993).

F. Potential roles for PET

Screening strategies using mammography and breast physical examination are widely available. Mammography is relatively expensive (on a population basis), requires high levels of technical expertise, and detects only 95% of breast cancers but has been validated in large randomized trials (Blamey, et al., 1994; Morrison, 1993). The number of women receiving mammography is increasing: the percentage of women over 40 years of age who had ever obtained at least one mammogram rose from 38% in 1987 to 60% in 1990, and the percentage of women who had a mammogram in the previous year rose from 17% to 33%.

PET researchers (e.g., Adler, 1993) acknowledge that the high cost (and limited availability) of PET argue against its potential to replace mammography for screening large populations of asymptomatic women. However, other potential applications of PET in the management of patients with breast cancer have been defined in the literature:

- screening in subgroups of women, e.g., those with breast implants (Wahl, et al., 1994), and those with prior breast radiotherapy, multiple breast masses and history of negative biopsy results, or severe fibrocystic disease (Tse, et al., 1992);

- monitoring response to chemotherapy (Wahl, et al., 1993; Tse, et al., 1992);

- nonsurgical evaluation of breast disease (Tse, et al., 1992; Adler, et al., 1993; Avril, et al., 1996b; Scheidhauer, et al., 1996);

- selection of patients for axillary dissection and for preoperative chemotherapy (Tse, et al., 1992; Adler, et al., 1993; Avril, et al., 1996a; Scheidhauer, et al., 1996)

- quantification of tumor glycolytic rate as a prognostic factor (Tse, et al., 1992; Avril, et al., 1996b).

II. RESULTS

Twenty-three articles from MEDLINE and other database searches and from the bibliographies of initially retrieved articles were selected as meeting the screening criteria. After review, 13 (56%) met inclusion criteria for assignment to the following levels of the diagnostic efficacy hierarchy (Fryback and Thornbury, 1991; *Appendix 2: Assessing Diagnostic Technologies*): 8 met the definition of technical efficacy (See reference list; full data abstraction tables for technical efficacy studies are on file with the MDRC Technology Assessment Program) and 5 met most or all of the evidence-based criteria for studies of diagnostic accuracy (Table 3). Table 2 summarizes cross-

study findings on PET and alternative technologies. These studies have methodologic limitations, and accordingly were not combined statistically for this review.

The potential uses of PET in breast cancer outlined above have been addressed only anecdotally or in studies that should be considered preliminary. Subgroup screening has been studied in two patients with breast implants (Wahl, et al., 1994) and in 3 patients with radiodense breasts (in a series of 14 reported by Tse, et al., 1992). Changes in tumor glucose metabolism during chemotherapy have been reported in small series of patients (Bassa, et al., 1996; Bruce, et al., 1995; Jansson, et al., 1995; Mortimer, et al., 1996; Wahl, et al., 1993). Correlation of tumor glycolytic rate to other prognostic features were studied by Avril, et al., (1996b) with no association established.

Studies presented below addressed the non-invasive determination of primary breast disease and axillary lymph node involvement using FDG PET. One small case-control study was identified (Nieweg, et al., 1993) and was included, in spite of its small size. The remaining studies were series of patients who presented for surgical evaluation of breast masses; patients without disease within the series were internal controls used for comparison. Patients evaluated for axillary node involvement were accrued from those with malignant primary breast disease, and patients with benign nodal disease served as internal controls.

All patients in these case series had suspected or biopsy-proven breast cancer, and relatively low proportions of patients had benign lesions. Therefore, the pre-test probability of disease in the study populations was high. Variations in reporting across studies with respect to unit of analysis (by patient, lesion or axillae) and extent of disease (size of primary tumor and level of axillary lymph node involvement) may further affect the generalizability of these results. All studies provided information on the comprehensiveness of blinding of the test interpreters to the gold standard. However, none of these studies met strict evidence-based criteria for blinding, because determination of the diagnostic gold standard independent of the PET results could not be ascertained. This will likely result in significant bias and inflated estimates of accuracy. These results should be interpreted accordingly.

A. Defining primary breast disease

Adler, et al., (1993) and Avril, et al., (1996b) assessed the ability of PET to detect primary breast disease both quantitatively and qualitatively. Nieweg, et al., (1993b) used a case control design, but failed to report information on criteria for judging images positive or negative for cancer and used only one image interpreter. No data on alternative technologies were presented. Variations in blinding of the image readers to either the gold standard or to other clinical information and in choice of a retrospectively determined cut-off used in the quantitative analyses occurred across these studies. Only Scheidhauer, et al., (1996) reported operating characteristics for alternatives to PET, but the evaluation of clinical examination and mammography was not described with sufficient detail to be reproducible. These studies have limitations in reporting and study design and should be considered preliminary.

B. Defining axillary lymph node involvement

Adler, et al., (1993) and Scheidhauer, et al., (1996) assessed a small subset of patients with malignant primary breast cancer for axillary lymph node involvement but reported no data on alternative technologies. Avril, et al., (1996a) presented results in a larger group of patients combined with results from 10 patients with benign primary breast disease to compare the accuracy of PET to clinical exam. Subgroup analyses according to primary tumor stage were conducted for PET but not for clinical examination. Results were presented as point estimates with 95% confidence intervals, which ranged widely due to small study size. These results should be interpreted with caution.

C. Detecting distant metastases

Scheidhauer, et al., (1996) also reported anecdotal evidence on a subgroup of 8 patients (23 total lesions) with distant metastases at the time of diagnosis. Small study size and limitations in study design suggest that these results should be considered preliminary.

III. SUMMARY

Preliminary studies into the role of FDG PET in the diagnosis and management of breast cancer have been reported in the literature. Table 2 summarizes findings from these studies on the diagnostic accuracy efficacy of PET. These studies received low methodology grades because of limitations in blinding, small study size, and incomplete reporting. The MDRC Technology Assessment Program did not identify any published studies that documented PET imaging at higher levels of the diagnostic efficacy hierarchy.

Only one study (Nieweg, et al., 1993) used a case control design; the remaining studies were uncontrolled or used small numbers of internal controls. None of the studies met strict evidence-based criteria for evaluation of diagnostic tests. The prevalence of malignancy in these study populations is high, may be weighted toward severe disease, and may not provide accurate estimates of accuracy. Predictive values should be interpreted accordingly. These data are further complicated by variations in reporting with respect to the unit of analysis (by patient, lesion, or axillae) and extent of disease (primary tumor size and level of axillary node involvement), and may not be generalizable to a population of mammographically tested patients with a lower prevalence of malignancy. All authors stressed the preliminary nature of these results and recommend assessment of PET in larger trials.

IV. DISCUSSION

The studies in Tables 2 and 3 report accuracy findings for detecting axillary lymph node involvement. Axillary dissection with histopathology of dissected nodes supplies information critical to subsequent treatment decisions, is currently recommended by the NCI for most patients with Stage 1 or higher disease, but is associated with significant morbidity. Under investigation are less invasive surgical methods and improved imaging modalities, including PET, which are used to map axillary lymph node involvement. However, selecting patients for axillary dissection based on PET studies would be extremely premature given the currently available PET research data. Published PET data are based on very small numbers of patients (compared to the tens of thousands who have enrolled in studies of screening and treatment options) and should be confirmed in larger, more rigorous studies before being incorporated into clinical practice. The efficacy of chemotherapy in patients with positive nodes has been demonstrated in large,

randomized trials; inappropriate assignment of patients to no chemotherapy (or to unneccessary exposure to the morbidity of chemotherapy) in the absence of axillary dissection should be avoided.

Future PET research in breast cancer is likely to involve improvements to resolution and diagnostic performance. High resolution positron emission mammography is under development (Thompson, et al., 1995), Although they do not report using the technology in patients, these authors hypothesize that this modification to existing PET technology will be an adjunct to conventional mammography and may eventually be an alternative to needle or surgical biopsy.

A. Alternatives to PET in some of its potential breast cancer applications

As noted above, improvements to breast cancer imaging and patient management are areas of intense research activity. Mammography in asymptomatic women is associated with a high sensitivity but a high yield of false positive results, a low positive predictive value, and a low specificity. However, technical improvements, increasing experience of radiologists who specialize in screening, and quality assurance criteria are increasing the accuracy of mammography and the diagnostic yield of subsequent procedures in established, high quality screening programs (Tubiana, et al., 1994).

Adler and Wahl (1995) review new methods for imaging the breast which may correct some of the shortcomings of mammography. These methods address both detection and classification of breast lesions, and include MRI of the breast, digital mammography, computer aided diagnosis, SPECT, and PET. These authors confirm that all of these methods would require significant technical refinement before replacing mammography for the detection of breast cancers.

The classification of mammographically detected lesions as benign or malignant (i.e. improving the specificity of mammography) is a particularly fertile area for continued research. As many as 70% and 85% of women who receive biopsies based on suspicious mammographic findings have benign conditions (Parker, et al., 1995). A non- or less invasive method for evaluating breast disease prior to biopsy which would reduce the number of surgical biopsies for benign lesions is desirable.

According to a review by Harms, et al., (1994), studies using MRI of the breast have demonstrated consistent contrast enhancement of malignant lesions and the lack of contrast enhancement of benign conditions. MRI used before surgical biopsy has been demonstrated to have a high negative predictive value and the ability to reduce the number of biopsies performed for benign lesions. Technical advances, such as dynamic contrast imaging, which will improve the diagnostic performance characteristics of breast MRI, are under investigation.

Biopsy techniques that are less invasive than open surgical biopsy, and that would reduce the adverse effects of unnecessary open biopsy procedures on health care resources and patients' psychosocial well-being, have been developed and have diffused into many health care settings. Stereotactic mammography to localize suspicious breast lesions, followed by fine needle aspiration or large needle core biopsy, are among these techniques. The equipment for these procedures is marketed in the United States. An analysis of over 6000 solid core biopsy results in the United States has recently been published; the authors concluded that the procedure is a reproducible and reliable alternative to surgical biopsy (Parker, et al., 1994). Tubiana, et al., (1994) report that fine needle aspiration cytology, in combination with increasing radiological expertise, can lead to malignant/benign biopsy ratios in specialist centers of between 3/1 and 10/1, minimizing the number of unnecessary benign biopsies.

B. A breast cancer research agenda

Given the population impact of breast cancer, it is reasonable to consider both new and existing screening, diagnostic (including PET), and treatment technologies within the context of the overall knowledge base and a strategic research agenda. Such an approach could provide a framework for evaluating the technologies' population and societal impacts.

The Institute of Medicine (IOM), in a 1993 report to the U.S. Army Medical Research and Development Unit on strategies for managing the breast cancer research program, lists the deficiencies in the current knowledge base on breast cancer. These include: biologically based treatments directed at precise targets are tantalizingly possible, but require major continuing research efforts; no dominant etiology for breast cancer has emerged from extensive epidemiologic studies, making it unlikely that quick and easy prevention strategies can be implemented; access to screening and treatment is problematic for minority women; the currently available treatments are less than completely effective and exact a substantial physical and emotional toll on the women who receive them; breast cancer is a very heterogeneous disease and it remains difficult to determine with any certainty the best therapeutic regimen for any particular woman; and far too few data are available to assess the effectiveness of various therapeutic interventions or how best to deliver them.

In response to the deficiencies in the knowledge base listed above, the IOM developed the following questions to guide research:

- What genetic alterations are involved in the origin and progression of breast cancer?

- What are the changes in cellular and molecular functions that account for the development and progression of breast cancer?

- How can endogenous and exogenous risk factors for breast cancer be explained at the molecular level?

- How can investigators use what is known about the genetic and cellular changes in breast cancer to improve detection, diagnosis, prevention, treatment, and follow up?

- What is the impact of risk, disease, treatment, and ongoing care on the psychosocial and clinical outcomes of breast cancer patients and their families?

- How can investigators define and identify techniques for delivering effective and cost-effective health care to all women to prevent, detect, diagnose, treat, and facilitate recovery from breast cancer?

The IOM felt that these questions offered a usable framework for defining the goals of a research program and evaluating the relevance of proposed research.

V. SUGGESTIONS FOR FURTHER RESEARCH

Breast cancer offers a somewhat different context for an evaluation of the potential roles of PET than do some of the other oncology indications for PET that are addressed in this report. Breast cancer makes a substantially larger contribution to potential years of productive life lost in the general population than do the other malignancies, and consumes a proportionate amount of health care resources. Mammography is among the only screening tests in routine use that is supported by evidence from large randomized clinical trials. Finally, a greater number of competing technologies (including those that improve the results of mammography) are under development.

Veterans Health Administration breast cancer research efforts could focus on questions similar to those of the IOM. Proposals to apply PET imaging to clinical management of breast cancer patients could then be evaluated within that framework.

Table 1 Breast cancer staging, treatment options, and survival

Stage	*Pathologic description*		*Treatment options*	*5-year survival*
0	carcinoma in situ • nonpalpable lesions discovered on screening mammography • accounts for 15 - 20% of all breast cancers	intraductal • presents as mammographic microcalcifications or a soft tissue abnormality	• mastectomy with excision of lymph nodes around axillary tail of breast (but without a formal axillary dissection) results in a local and distant recurrence rate of 1 - 2% • conservative surgery with radiotherapy results in recurrence rate of 9 - 21% • salvage of recurrences is feasible, with survival comparable to upfront mastectomy	> 95%
		lobular • generally widely distributed throughout breast and frequently bilateral • indicates 25% chance of developing invasive cancer within 25 years	• clinical management controversial; options include no treatment after biopsy with careful follow up, or bilateral prophylactic mastectomy • axillary dissection not necessary • patients who have undergone local excision are eligible for a large multicenter RCT of tamoxifen to prevent development of invasive cancer	
I	- tumor ≤ 2.0 cm in greatest diameter - no regional lymph node metastases - no distant metastases		• 21% of patients managed with surgery alone may ultimately relapse • breast conserving surgery followed by radiation therapy provides tumor control equivalent to more extensive surgical procedures; approximately 20% of patients experience local recurrence • axillary dissection should be performed • suitable ER negative patients receive adjuvant chemotherapy with a proven effective regimen; a group of patients with small tumors who do not benefit from adjuvant therapy may be identified • ER positive patients receive adjuvant tamoxifen	85%
II	• tumor > 2cm but ≤ 5 cm in greatest diameter • no nodal metastases, or metastases to movable ipsilateral axillary nodes • no distant metastases	negative nodes	• survival is equivalent with any of the surgical options (mastectomy, mastectomy with reconstruction, or conservative surgery plus radiation therapy) • radiation therapy to the chest wall and regional nodes should be considered for patients at high risk of local recurrence (with known residual disease) • adjuvant combination chemotherapy with a proven effective regimen for both pre- and post-menopausal ER negative patients • adjuvant tamoxifen with established schedule for ER positive patients • optimal adjuvant therapy has not been defined for any subset of patients; all patients and their physicians are strongly encouraged to participate in controlled clinical trials	66%
		positive nodes	• survival is equivalent with any of the surgical options (mastectomy, mastectomy with reconstruction, or conservative surgery plus radiation therapy) • radiation therapy to the chest wall and regional nodes should be considered for patients at high risk of local recurrence (with known residual disease or 4 or more involved nodes) • adjuvant combination chemotherapy with a proven effective regimen for both pre- and post-menopausal patients • tamoxifen, either alone or combined with chemotherapy, prolongs DFS when administered for 24 months to postmenopausal women with axillary node metastases • optimal adjuvant therapy has not been defined for any subset of patients; all patients and their physicians strongly encouraged to participate in controlled clinical trials	

Stage	*Pathologic description*		*Treatment options*	*5-year survival*
III	• tumor any size • metastases to movable ipsilateral axillary nodes or metastases to ipsilateral nodes fixed to one another or to other structures • no distant metastases	operable	• modified radical mastectomy or radical mastectomy • radiation therapy • combination chemotherapy with or without hormones is given in conjunction with surgical and radiotherapeutic procedures • tamoxifen as postoperative adjuvant hormonal therapy for postmenopausal patients with high ER and PR levels is under investigation	41%
		inoperable	• newly diagnosed patients should be considered candidates for one of the clinical trials in progress to improve therapeutic results • incisional biopsy followed by radiation to primary tumor and regional lymph nodes • combination adjuvant chemotherapy • if chemotherapy is contraindicated, hormonal therapies may be used for patients whose tumors are ER and PR positive after surgery and radiotherapy • initial chemotherapy followed by surgery and/or radiation therapy is under investigation • phase II studies evaluating new chemotherapeutic or biologic agents may be considered for patients whose local disease is not controllable by other means	
IV	• tumor any size • any pattern of axillary lymph node metastases • distant metastases present		• all patients with stage IV disease should be considered candidates for one of the ongoing clinical trials to improve therapeutic results • surgical biopsy • in patients with ER and PR positive tumors and no visceral disease, hormonal therapy is used • in patients with ER and PR negative tumors or visceral disease, combination chemotherapy is used	10%
Recurrent	localized recurrence after breast conserving surgery	• subset of good prognosis patients with locally recurrent disease in the breast at 1-9 years post lumpectomy plus radiotherapy	• salvage mastectomy plus radiotherapy	65-80%
	other/widespread recurrence	• visceral disease absent, ER and PR positive or unknown, disease free interval > 2 years	• hormonal therapy/oophorectomy for premenopausal patients • antiestrogen/progesterone therapy with tamoxifen for postmenopausal patients	treatment is palliative
		• recurrence localized or visceral	• surgery and/or radiotherapy	treatment is palliative
		• relapse after response to additive hormonal therapy	• other forms of hormonal therapy not previously used	treatment is palliative
		• visceral disease, ER and PR negative, or disease free interval < 2 years	• combination chemotherapy	treatment is palliative

Abbreviations: RCT, randomized controlled trial
DFS, disease free survival
ER, estrogen receptor
PR, progesterone receptor

Table 2 Summary of the Literature: Diagnostic accuracy efficacy studies of PET and alternatives in breast cancer

Notes: All studies except Nieweg, et al., (1993b), which was a case-control study, were series of patients presenting for surgical evaluation of breast masses (a high index of suspicion of malignant disease) and included internal controls as the comparison group. Predictive values should be viewed accordingly. Studies assessing axillary node involvement included patients with malignant primary breast disease. Results from Avril, et al., (1996b) were reported as ranges of data from all subgroup analyses. Results from Avril, et al., (1996a) included all patients with benign and malignant primary disease and represent 95% confidence intervals; subgroup analyses were not reported because of their small study size. None of these studies met strict evidence-based medicine criteria for blinding, but all studies provided data on the comprehensiveness of blinding of test interpreters to the gold standard.

Where substantial duplication in purpose of study, patients studied, and results in multiple studies from the same institution could be inferred, only the most recent, largest, most rigorously designed, or most comprehensive was included in the table. Although data from both studies by Avril and associates (1996a and 1996b) represent the same patient population, these studies addressed different purposes; inclusion of both publications was felt to be warranted.

Abbreviations are listed at the end of the table.

Role (Note: some studies assessed multiple roled)	Study	N	Operating Characteristics*			Evidence-Based Medicine Criteria**			Methodologic Quality Grade***
			PET	Clinical Exam	Mammography	comparison group	histologic gold standard	blinding	
Defining primary disease	Adler, et al., 1993	27 positive lesions 8 negative lesions	Se=96% Sp=100%			+ internal	+	+	C
	Nieweg, et al., 1993b	11 cases 8 controls	Se=91% Sp=100%			+	+	+	C
	Avril, et al., 1996b	41 positive lesions 31 negative lesions	Se=68%-94% Sp=84%-100% PPV=87%-97% NPV=70%-93%			+ internal	+	partial	D
	Scheidhauer, et al., 1996	23 malignant cases 7 benign cases	Se=91% Sp=86%	Se=74% Sp=71%	Se=86%	+ internal	+	partial	D
Defining axillary node involvement	Adler, et al., 1993	9 positive axillae 10 negative axillae	Se=90% Sp=100%			+ internal	+	+	C
	Avril, et al., 1996a	24 positive axillae 27 negative axillae	Se=57%-93% Sp=81%-100% PPV=75%-100% NPV=66%-100%	Se=36%-78% Sp=66%-96% PPV=30%-70% NPV=51%-85%		+ internal	+	+	C
	Scheidhauer, et al., 1996	9 malignant cases 9 benign cases	Se=100% Sp=89%			+ internal	+	partial	D
Detecting distant metastases	Scheidhauer, et al., 1996	8 positive lesions 15 negative lesions	Se=100% Sp=100%			+ internal	+	partial	D

N, number of study subjects included in analysis; unless otherwise noted, data are analyzed by subject
Se, sensitivity
Sp, specificity
PPV, positive predictive value
NPV, negative predictive value

* operating characteristics defined in *Appendix 2: Assessing Diagnostic Technologies, page 5-7*
** *Appendix 2, page 8*
^^^ *Appendix 2, page 9*

Table 3 Diagnostic efficacy of FDG PET and alternatives in breast cancer

Note: All of the studies in this table met most of the evidence-based medicine criteria for diagnostic test evaluations. Nieweg, et al., (1993b) was included (in spite of its small number of breast cancer cases) because it is a case-control study. All other studies are case series with internal controls (i.e., patients with benign primary masses or benign axillary nodes), and it was possible to calculate sensitivity and specificity for PET in those studies; however, all of these patients had suspected breast cancer and relatively low proportions of patients had benign lesions, making the pre-test probability of disease in the study populations very high. Accordingly, predictive values were only reported for both studies by Avril and associates (1996a and 1996b), because there was roughly an equivalent proportion of malignant and benign disease. Studies assessing axillary node involvement included subsets of only those patients with malignant primary breast disease from corresponding case series.

Where substantial duplication in purpose of study, patients studied, and results in multiple studies from the same institution could be inferred, only the most recent, largest, most rigorously designed, or most comprehensive was included in the table. Although data from both studies by Avril and associates (1996a and 1996b) are derived from the same patient population, these studies addressed different purposes, and inclusion of both was felt to be warranted.

All studies in the table compared PET to the "gold standard" of histopathology of surgical specimens, which is the reference test for the operating characteristics reported in the "Results/Comments" column.

Abbreviations are listed at the end of the table.

Study	***Patients/Methods***	***Results/Comments***
Adler, et al., 1993 *University Hospitals of Cleveland*	**Purpose** • to determine the relationship between FDG uptake and tumor histology in patients with newly discovered breast masses • to determine the ability of PET to detect axillary node metastases prior to dissection **Cases** 28 patients with newly discovered breast masses ≥ 1 cm in diameter • 35 breast lesions (27 malignant, 8 benign) • 19 axillae from 18 patients (9 malignant, 10 benign) • first consenting patients who could be scheduled for PET prior to biopsy **Methods** • all subjects received breast PET scans after 4 hour fasts • 25/28 had surgical biopsy • 3/28 had fine needle aspiration • 19 patients diagnosed with breast cancer subsequently underwent PET scanning of axillary region and axillary dissection • PET results compared to histopathologic findings • PET image readers were blinded to pathologic and axillary dissection findings, but were not blinded to physical exam or mammography results • single consensus visual/qualitative interpretation (5 point scale, with 4 or 5 scored as malignant) • quantitative (DUR) measures of FDG uptake obtained with ROIs **Study design limitations** • numbers of cases and internal controls not equivalent (high prevalence of malignancy) • blinding of readers to gold standard, but not to exam or mammography • comprehensiveness of nodal sampling not indicated	**Quantitative analyses** • benign cysts (mean DUR = 0.2 ± 0.3) had diminished FDG uptake • solid benign lesions, mean DUR = 1.8 ± 0.5 • malignancies, mean DUR = 12.8 ± 9.3 • cut point DUR = 2.4 retrospectively found to discriminate benign vs malignant lesions (p = .0005) • cut point DUR = 1.0 retrospectively found to discriminate between cystic and solid benign lesions • within malignancies, DUR was significantly correlated with histologic grade (Spearman rho = .55, p = .006) **Diagnosing primary disease (27 malignant, 8 benign)** Se = 96%; Sp = 100% (based on qualitative scores) **Axillary node involvement (9 cases, 10 controls)** Se = 90%; Sp = 100% (based on qualitative scores) **Authors' comments** • high cost means that PET is unlikely to be used in screening • may eliminate need for biopsy in patients with mammographically indeterminate or occult lesions • patients with high pre-biopsy probability of disease (based on PET) might be spared a diagnostic procedure and proceed directly to definitive therapy • PET may impact management by indicating which patients have axillary nodal involvement • high specificity cannot be generalized to population of all women with breast masses ≥ 1 cm (due to high prevalence of malignant disease in sample)

Study	*Patients/Methods*	*Results/Comments*
Nieweg, et al., 1993b *M.D. Anderson Cancer Center, University of Texas*	**Purpose** to investigate the sensitivity and specificity of FDG in the detection of breast cancer **Cases** • 11 patients with biopsy-confirmed breast cancer (including one with both cancer and fibrocystic disease) • median size of tumors was 2.5 cm **Controls** 8 subjects without cancer (including 3 with previous mastectomy but currently disease free, one with 2 cysts, 3 healthy volunteers, fibrocystic lesion from one of cases) **Methods** • all subjects scanned after 4 hour fasts • TNT ratios calculated using contralateral breast and ROIs • one image reader who was blinded to clinical findings **Limitations of study design** • comprehensiveness of nodal sampling not indicated • qualitative image interpretation implicit, but criteria for judgment re presence of disease not given	**Diagnosing primary disease** • *Se = 91%; *Sp = 100% • single false negative in patient with 1 cm tubular carcinoma associated with focus of invasive ductal carcinoma • TNT ratios of tumors from 1.0 to 15.3 (median 4.9) **Axillary node involvement** • due to limitations in axial field of view, only 5 patients evaluated for axillary involvement with PET • TNT ratios for nodes from 2.1 to 29.4 **Authors' comments** • PET images easy to evaluate: no equivocal results, myocardial uptake did not interfere with image interpretation • no adverse reactions to FDG • unclear whether TNT ratios are adequate for monitoring response to chemotherapy
Avril, et al., 1996a *Technische Universität, Munich, Germany*	**Purpose** to evaluate preoperatively the diagnostic accuracy of PET for detecting axillary lymph node metastases in women with suspected breast cancer **Cases** 51 women with newly discovered breast tumors who were scheduled to undergo surgery • primary disease: 41 malignant, 10 benign • axillary lymph node status assessed in patients with malignant primary tumor, excluding 4 with locally advanced disease: 24 malignant, 17 benign **Methods** • all patients fasted for at least 4 hours before PET • SUVs calculated • images analyzed qualitatively by two independent interpreters blinded to other diagnostic tests • criterion for positive PET study: foci of increased FDG uptake reached by consensus • criterion for positive clinical exam: detection of enlarged, palpable lymph nodes or conglomerate masses in the axilla • axillary lymph node status confirmed by histopathology • PET and CE compared to histopathology **Limitations of study design** • number of cases and internal controls not equivalent (high prevalence of malignancy) • comprehensiveness of nodal sampling unclear • independence of test result and determination of final diagnosis unclear	**Detecting axillary node involvement (24 malignant, 27 benign)** *overall (reported with 95% CI)* PET: Se=79% (57%-93%); Sp=96% (81%-100%); PPV=95% (75%-100%); NPV= 84% (66%-95%) Clinical Exam: Se=58% (36%-78%); Sp=85% (66%-96%); PPV=78% (30%-70%); NPV= 70% (51%-85%) • includes 10 with benign primary disease **Detecting axillary node involvement (6 malignant, 12 benign)** *Stage pT1 only (reported with 95% CI)* PET: Se=33% (4%-78%); Sp=100% (73%-100%); PPV=100% (15%-100%); NPV= 75% (47%-93%) **Detecting axillary node involvement (18 malignant, 5 benign)** *Stage > pT1 (reported with 95% CI)* PET: Se=94% (72%-100%); Sp= 100% (47%-100%); PPV=100% (80%-100%); NPV= 83% (35%-100%) **Authors' comments** • smallest tumor-infiltrated lymph node visualized by PET was 0.8 cm in diameter • sensitivity of PET imaging of axillary lymph node depends on extent of lymph node involvement (unable to verify due to small numbers) • spatial resolution and partial volume effect limit assessment of small axillary lymph nodes • further studies are needed to compare accuracy and cost-effectiveness of PET with other imaging methods available for staging procedures • authors reported an increased sensitivity of PET with an increased number of involved lymph nodes

Study	*Patients/Methods*	*Results/Comments*
Avril, et al., 1996b *Technische Universität München, Munich, Germany*	**Purpose** • to evaluate the ability of PET to differentiate malignant versus benign breast tumors using visual and quantitative analysis • to compare regional FDG uptake in breast cancer with histology • to correlate FDG uptake with grade and size of tumors, estrogen receptor (ER)/progesterone (PR) status and rate of cell proliferation **Cases** 51 women with 72 proven breast lesions (41 malignant, 31 benign) who presented with abnormal mammography or palpable breast lesions and who were scheduled to undergo surgery • patients with prior breast surgery within the last 3 months or who had undergone chemotherapy or radiation therapy • size of breast lesions ranged from 0.3 cm to 9.0 cm (mean diameter= 2.5 cm ± 1.8 cm **Methods** • patients fasted for at least 4 hours before PET • all patients studied in prone position • ROIs over all histologically proven breast lesions identified; for lesions that could not be clearly identified by increased FDG uptake, surgeon's report used to position ROI • SUVs calculated for all histologically confirmed breast tumors; partial volume correction calculated • PET visual analysis reached by consensus performed by two observers blinded to clinical history, examinations, and histology; regional FDG uptake classified as unlikely, probable, and definite • ROC curves, correlations of FDG uptake and tumor size, blood glucose level, cell proliferation, histopathologic grading ER and PR performed only in tumors > 1 cm in size **Limitations of study design** • number of cases and internal controls not equivalent (high prevalence of malignancy) • partial blinding of PET readers to data in surgeon's report used for anatomical positioning	**Diagnosing primary disease using visual analysis** *including all lesions regarded as definite and probable malignant* Se=83%; Sp=84%; PPV=87%; NPV=87% *including only those lesions with definite malignant findings* Se= 68%; Sp=97%; PPV=97%; NPV=70% *including lesions >1 cm regarded as definite and probable malignant* Se=94%; Sp=84%; PPV=87%; NPV=93% *including lesions > 1 cm regarded as definite malignant findings* Se=78%; Sp=97%; PPV=97%; NPV=79% **Quantitative analysis** *expressed as mean ± SD* malignant = 3.3 ± 1.8 vs. benign= 1.4 ± 0.5 ($P < .01$) *from ROC analysis, using threshold SUV of 2.5* Se=75%; Sp=100% *from ROC analysis, using threshold SUV of 2.5*, with partial volume correction Se=92%; Sp=97% • differences between corrected and uncorrected SUV values not statistically significant **Other findings** • the reproducibility of ROI positioning in a subset of 20 patients was elevated; interobserver variability was $r= .91$, intraobserver variability was $r= .96$ • no statistically significant correlation found between partial volume-corrected SUV values of invasive breast cancer and tumor size, blood glucose level, tumor-cell proliferation and histopathologic grading • higher SUV values for ER-negative tumors compared with ER-positive tumors, but not statistically significant • no statistically significant correlation between SUV values of breast cancer and PR status **Authors' comments** • partial volume effects in tumors < 1 cm in size limits detection by PET • in situ carcinoma showed an increase in FDG uptake lower than that of invasive cancer, but further study in larger populations are needed • further studies are needed to determine the prognostic value of FDG uptake in breast cancer

Study	*Patients/Methods*	*Results/Comments*
Scheidhauer, et al., 1996 *University of Cologne and Max-Planck Institut for Neurological Research, Cologne, Germany)*	**Purpose** • to assess the diagnostic accuracy of qualitative PET scans • to demonstrate imaging results in a manner acceptable to referring clinicians • to minimize scanning time and patient discomfort **Cases** 30 patients with suspicion of breast cancer based on clinical exam or mammography/ ultrasonography (23 malignant, 7 benign) • 18 of whom also had ipsilateral axillary node exploration; no axillary exploration done in 5 patients with locally advanced disease who received neoadjuvant chemotherapy before surgery • 8 patients with distant metastases at the time of diagnosis **Methods** • patients fasted at least 12 hours before PET • PET scans performed on patients in the supine position • attenuation-corrected emission images and transmission images available to investigator; data displayed on computer screens as 3 orthogonal images and with interactive choice of slice localization by investigator; data also viewed by Multi Purpose Matching (MPM) software • qualitative PET images evaluated by two readers, blinded to all information other than that the patient was scheduled for breast surgery • surgery performed between 1 and 5 days after PET scans • all breast lesions biopsied; additional foci of increased FDG uptake not corresponding to area of suspicion on other imaging also biopsied • PET, clinical exam, and mammography compared to histology **Limitations of study design** • number of cases and internal controls not equivalent (high index of suspicion for malignancy) • PET results and determination of disease status not independent • study design methods (i.e., blinding) for mammography and palpation not described	**Detecting primary tumors (23 malignant, 7 benign)** PET: Se=91%; Sp=86% Mammography: Se=86% Clinical exam: Se=74%; Sp=71% **Detecting axillary lymph node involvement (9 malignant, 9 benign)** PET: Se=100%; Sp=89% **Detecting distant metastases (8 positive, 15 negative; 8 total patients in the PET field of view)** PET: Se=100%; Sp=100% **Authors' comments** • a more time-effective qualitative approach does not decrease the accuracy of breast cancer detection • MPM software did not enhance accuracy when compared with standard displays of orthogonal slices (no data reported) • combination functional scan with anatomical scan showed higher acceptance by referring physician and improved intraoperative orientation, thereby facilitating the identification and correct removal of the area of interest (no data reported) • supine position during imaging reflects position during surgery • because of selection criteria, accuracy data cannot be used to judge the accuracy of these techniques, but FDG PET may yield additional information on tumor biology • authors suggest PET is comparable to other imaging techniques with respect to imaging time and scanning discomfort • authors suggest roles for PET in patients with inconclusive findings prior to biopsy, for preoperative TMN staging in patients with highly suspicious breast findings to aid therapy planning, and to replace palpation and conventional imaging tools when they are technically not feasible (eg. in patients with silicone impants)

Abbreviations:
DUR, dose uptake ratio
Se, sensitivity
Sp, specificity
TNT, tumor to normal uptake ratio
SUV, standardized uptake value
ROI, region of interest

* indicates calculated by MDRC TA Program from data supplied in published article

VI. REFERENCES Background and studies meeting evidence-based medicine criteria for evaluations of diagnostic tests

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VIII. REFERENCES: Excluded studies

Exclusion criteria included:

- number of cases < 12
- duplicated or superseded by subsequent or concurrent study from the same institution
- radiopharmaceutical other than FDG
- gamma camera rather than PET
- tumors other than squamous cell carcinomas
- insufficient information to judge comparability of case and control groups, details of imaging protocol, whether visual or quantitative analysis of PET data used, or type of PET data analysis used
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